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Abstract: PURPOSE: Optimal atrioventricular delay (AVD) setting for cardiac resynchronisation therapy, i.e. biventricular pacing in patients with heart failure, remains a formidable challenge. Thus, the purpose of this study was to evaluate the effects of different AVD on inter- and intra-ventricular resynchronisation using phase histograms of radionuclide ventriculography (RNV). METHODS: In 17 consecutive patients (mean age 64 +/- 6 years), RNV was performed 236 +/- 350 days after pacemaker implantation for cardiac resynchronisation therapy. Images were acquired during atrial pacing at 80 bpm and during biventricular pacing with AVD ranging from 80 to 160 ms. Inter-ventricular dyssynchrony was measured by the delay between the mean phase angles of the left and right ventricles. Intra-ventricular dyssynchrony was measured by the standard deviation (SD) of left ventricular phase histograms. RESULTS: Left ventricular (LV) ejection fraction (EF) was inversely correlated to LV dyssynchrony (SD of LV phase histogram, R = -0.82, $p < 0.0001$). However, the increase in LVEF by biventricular pacing (mean +4.4 +/- 4%) showed only modest correlation to the resulting resynchronisation effect (characterised by a -13 +/- 8 degrees decrease in LV phase histogram SD, R = -0.38, $p < 0.0001$). CONCLUSION: RNV is helpful in optimising pacing parameters for resynchronisation therapy. Varying AVD did not have a major impact on intra- or inter-ventricular resynchronisation. Thus, the benefit of AVD-based LVEF optimisation seems to result from atrioventricular resynchronisation.

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ORIGINAL ARTICLE

Effects of AV delay programming on ventricular resynchronisation: role of radionuclide ventriculography

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Abstract
Purpose Optimal atrioventricular delay (AVD) setting for cardiac resynchronisation therapy, i.e. biventricular pacing in patients with heart failure, remains a formidable challenge. Thus, the purpose of this study was to evaluate the effects of different AVD on inter- and intra-ventricular resynchronisation using phase histograms of radionuclide ventriculography (RNV).
Methods In 17 consecutive patients (mean age 64±6 years), RNV was performed 236±350 days after pacemaker implantation for cardiac resynchronisation therapy. Images were acquired during atrial pacing at 80 bpm and during biventricular pacing with AVD ranging from 80 to 160 ms. Inter-ventricular dyssynchrony was measured by the delay between the mean phase angles of the left and right ventricles. Intra-ventricular dyssynchrony was measured by the standard deviation (SD) of left ventricular phase histograms.
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Conclusion RNV is helpful in optimising pacing parameters for resynchronisation therapy. Varying AVD did not have a major impact on *intra*- or *inter*-ventricular resynchronisation. Thus, the benefit of AVD-based LVEF optimisation seems to result from atrioventricular resynchronisation.

Keywords Cardiology ventricular function · Imaging · Radionucluide ventriculography · Cardiac resynchronisation therapy

Introduction

In chronic congestive heart failure, dyssynchrony of left versus right ventricle (RV) as well as atrioventricular (AV) dyssynchrony add to progressive aggravation of the cardiac performance. In addition to optimised medical therapy, biventricular pacing devices have been shown to improve left ventricular (LV) function and prognosis by resynchronising LV and RV contraction [1]. However, the so-called cardiac resynchronisation therapy (CRT) not only acts via inter-ventricular and intra-ventricular resynchronizations [2, 3] but also allows to optimise the timing of atrial and ventricular systoles, i.e. AV resynchronisation [4, 5]. It has recently been shown that the LV dyssynchrony as assessed with gated single photon emission computed tomography (SPECT) may be used to predict response to CRT [6]. SPECT, however, may provide only limited information, as it only allows to assess the LV function, i.e. intra-ventricular dyssynchrony. By contrast, radionuclide ventriculography (RNV) has been successfully used not only to quantify LV, but also inter-ventricular dyssynchrony by analysis of phase histograms and their standard deviation (SD) in dilated cardiomyopathy [7, 8] as well as to assess

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the effects of biventricular pacing [9]. Although comprehensive CRT includes AV resynchronisation by left atrial pacing and RNV offers the unique opportunity (magnetic resonance imaging is not an option in patients with implanted devices) to assess the effects of different atrioventricular delays (AVDs) on inter- and intra-ventricular resynchronisations, this has not been assessed so far. Averaging a high number of cardiac cycles during AVD optimisation has the advantage of equalising the respiratory changes in contrast to the conventionally used beat-to-beat analysis of the echocardiographic [3] or haemodynamic response [10]. In addition, the global performance of contraction can be assessed, and fully automated image acquisition and calculation minimise operator bias. The purpose of this study was to assess the effect of AVD optimisation on *inter*- and *intra*-ventricular resynchronisations using phase images of RNV.

Methods

Patients

The subjects of this study were 17 consecutive patients undergoing CRT optimisation after a mean of 236±350 days post-implantation at our institution. Pre-implantation data were collected retrospectively and are summarised in Table 1. All patients had symptomatic congestive heart failure (New York Heart Association Classification≥2) and LV ejection fraction (EF)<35% associated with one of the following indications for CRT: complete AV block (AVB), complete left bundle branch block (LBBB) with QRS≥150 ms or AVB first degree≥220 ms associated with a QRS>120 ms either due to LBBB or bifascicular block (right bundle branch block+left anterior hemiblock in one patient). The RV lead had been implanted in the RV apex, the right atrial lead in the inter-atrial septum or in the right atrial appendage if necessary for sensing or stability reasons, and the LV lead was implanted into the posterolateral coronary sinus branch at the position with the latest electrical activation during RV pacing, after sampling at least three positions within more than one coronary sinus branch.

Table 1 Patient characteristics

Patients	n=17
Age (yrs, mean±SD)	64±6
Ischemic cardiomyopathy	10 (59)
Valvular heart disease	5 (29)
moderate to severe MR untreated	3
mechanical aortic valve replacement	1
mechanical aortic and mitral valve replacement	1
Nonischemic cardiomyopathy	2
LVEF (%, baseline echocardiography)	21 (7), range 11 to 35
EDVI (ml, baseline echo)	188±43
End-diastolic diameter (mm, baseline echo)	80±6
QRS LBBB (ms, n=13)	177±30
RBBB, LAHB+AVB1 (ms, n=1)	135
PQ interval (ms)	213±45
Severe AVB first degree (>250 ms)	2
Pacemaker dependent	3

Values are presented as n (%) unless otherwise indicated.
LVEF left ventricular ejection fraction, *EDVI* end-diastolic volume index, *LBBB* left bundle branch block, *RBBB* right bundle branch block, *AVB1* AV block first degree

Pacing protocol

To eliminate the effects of heart rate on resynchronisation, all patients were studied at paced rates of 80 bpm. Baseline images were obtained during intrinsic conduction in 12 patients and with RV pacing only at AVD 180 ms in three patients with complete AVB and in 2 patients with severe AVB first degree. Then, biventricular pacing was performed without inter-ventricular delay at different AVD (80, 100, 120, 140 and 160 ms) in random order to assess the best AVD for each individual patient. All patients had stable sinus rhythm with extrasystoles less than 2% according to the acquisition reports.

Radionuclide ventriculography

Erythrocyte labeling was performed using 1,000 MBq ^{99m}Tc-pertechnetate 30 min after an intravenous bolus of 11.9 mg pyrophosphate solved in 10 ml saline. All studies were acquired for 10–12 min with 64 frames per RR interval in the "best septal" left anterior oblique position using a Siemens Diacam scintigraphic scanner (Siemens AG, Erlangen, Germany). The electrocardiogram was monitored continuously to ensure R-wave gating of the QRS complex. Scintigrams were acquired for each patient in sinus rhythm and during biventricular pacing for each AVD. For a processing purpose, raw scintigraphic data were transformed to an ENTEGRA workstation (GE Medical Systems, Milwaukee, WI, USA). LV regions of interest were drawn manually at end-diastole and end-systole by two independent observers unaware of the study condition for calculation of inter-observer variability. After correction for background counts, LVEF was calculated by dividing the difference of end-diastolic counts (EDC) and end-systolic counts (ESC) by EDC:

$$\mathrm{LVEF} = (\mathrm{EDC} - \mathrm{ESC})/\mathrm{EDC}$$

Phase images were generated from the scintigraphic data using the PMOD software package (PMOD Technologies, http://www.pmod.com). As the time activity curve and the

ventricular volume curve have a configuration that approximates a cosine function, the first harmonic cosine term alone is a reasonable approximation. Thus, the time–activity curve of each LV pixel can be described by its phase and amplitude, in the form:

$$f(t) = A\ \cos(t + c)$$

where $f(t)$ represents the activity of any pixel as a function of time after the R-wave, A the amplitude of the fitted function, which is an index of how dynamically that pixel is contracting, c represents the phase shift (given as angle) of the cosine function, which is an index of the time in the cardiac cycle (total of 360°) when the pixel contracts relative to the R-wave.

The phase program computed the phase and amplitude of the first Fourier harmonic of the time–activity curve of each pixel in the field of view. The color-encoded phase image graphically demonstrates each motion phase of every LV region using a continuous rainbow color wheel, corresponding to phase angles from one R-wave (0°) to the following R-wave (360°). Thus, one cardiac cycle represents 360°.

Mean phase angles were computed for RV and LV blood pools as arithmetic mean phase angle for all pixels in the ventricular region of interest. The difference between LV and RV mean phase angle was used to calculate interventricular dyssynchrony (LV–RV delay). Intra-ventricular contractile synchrony was measured using the SD of the mean phase angle of the LV blood pool (Fig. 1).

Statistical analysis

Continuous variables are expressed as mean±SD and are compared using Student's t test. Correlations are expressed using Pearson's coefficients. Inter-observer variability for continuous measurements was assessed according to Bland and Altman. Comparison of repeat measurements was performed with analysis of variance statistic for repeat measurements. A statistical significance was assumed at $p<0.05$, and calculations were performed using a commercially available software package (SPSS 13.0 for Windows).

Results

In 17 patients with recent biventricular pacemaker implants, six series of images were obtained during baseline rhythm, i.e. with biventricular CRT pacing switched off (CRT off) and biventricular pacing switched on (CRT on) adding up to a total of 102 series. A time frame of 11.7 ms (64 frames per 750 ms) was obtained in all patients from which EF and phase histograms were calculated. LVEF values of the two observers showed an excellent correlation ($R=0.941$, $p<0.0001$, SEE=0.54) with narrow Bland–Altman limits of agreement (−4.9% to 6.9%).

Biventricular pacing acutely improved EF by 4.4±4% (range 0–15%) compared to CRT off. The best AVD was 135±40 ms, but showed a wide range from 80 ms AVD to intrinsic rhythm in one patient.

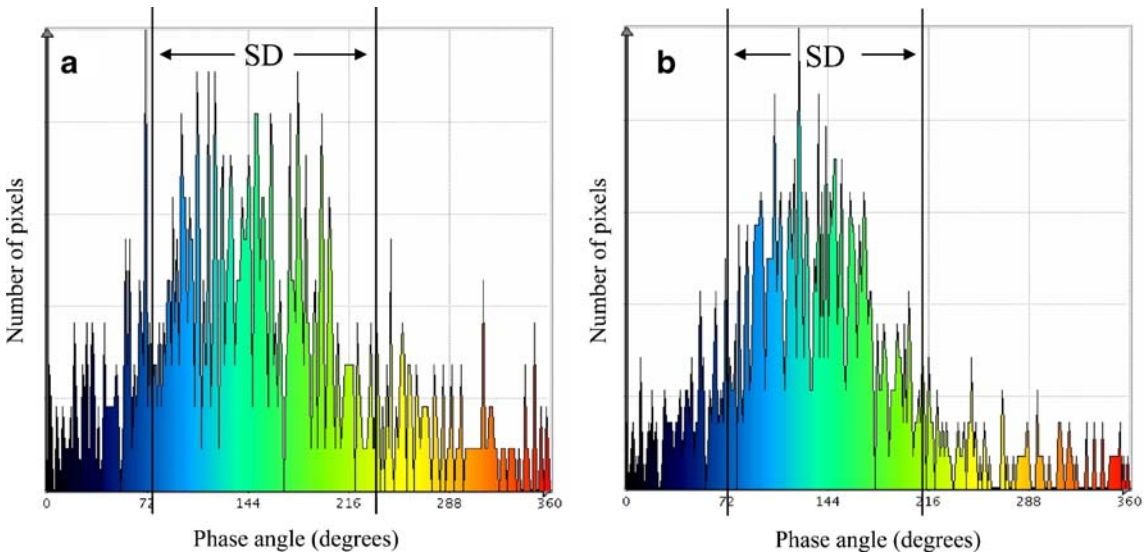

Fig. 1 Effect of CRT on intra-ventricular resynchronisation: phase histograms of the left ventricle illustrating dispersion of phase angles during ventricular ejection, plotted as phase angle (x-axis) versus number of pixels (y-axis). With CRT off, **a** there is large dispersion of the phase angle (155±78°) indicating LV dyssynchrony, while CRT **b** induces a substantial narrowing of the angle (141±68°) indicating effective resynchronisation. Both measurements were done in the same patient at a heart rate of 80 bpm

Relation of dyssynchrony to LV function and CRT effects

During RNV, the LVEF with CRT off correlated with baseline LV dyssynchrony expressed as the SD of the LV phase histogram (R=−0.82, p<0.001). This correlation was maintained when data from all six different AVD in each of the 17 patients (i.e. 102 measurements) were included (R=−0.82, p<0.001; Fig. 2). By contrast, the relation of LVEF to the inter-ventricular dyssynchrony (difference between mean LV and RV phase angle) was poor (R=0.27, p<0.01) and to the RV intra-ventricular dyssynchrony (SD of RV phase histogram) was lacking (R=0.13, p=0.2). At optimised AVD, the LVEF improved by a mean of 4.4±4% (range 0–15%, p<0.001), and the SD of the LV phase histogram decreased by a mean of 13±8° (range 3–31°, p<0.001). Although the improvement of LVEF was not related to the baseline LV dyssynchrony (SD of LV histograms, R=0.02, p=0.95), there was a modest but significant correlation with the improvement in resynchronisation of the LV (decrease in SD of LV phase histograms, R=0.38, p<0.0001). Changes in inter-ventricular dyssynchrony (RV–LV phase angle) or RV SD were not correlated to improvement in LVEF.

Relation of dyssynchrony to AVD programming

Mean baseline intra-ventricular LV dyssynchrony (SD of phase histogram) was significantly higher than during CRT at any AVD (Table 2, p<0.001). Furthermore, when analysing individual patients, the same pattern was observed: Baseline LV dyssynchrony improved by any AVD and changes in LVSD among different AVD were minor compared with the improvement from baseline (Fig. 3). This effect was similar in patients with intact AV conduction compared to patients with AVB.

The mean baseline inter-ventricular dyssynchrony also decreased significantly during CRT at any AVD (Table 2); however, when looking at individual patients, this effect was not consistent (Fig. 3). In six patients (Fig. 3), the inter-ventricular delay during CRT worsened, even though the intra-ventricular synchrony and LVEF improved by CRT. Resynchronisation of the right ventricle (SD of RV) was not observed during CRT compared to baseline values (Table 2).

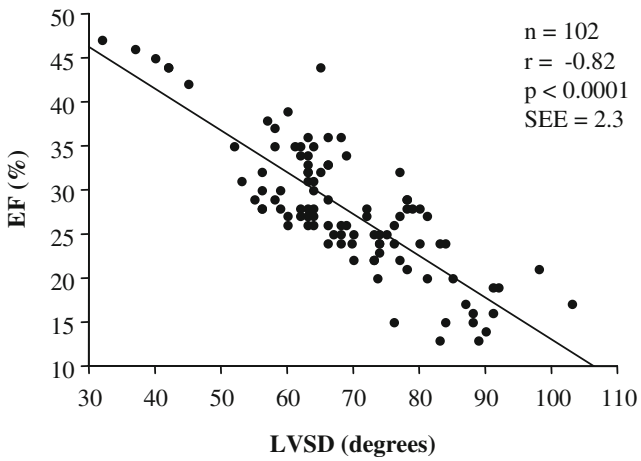

Fig. 2 There was a strong correlation between decreasing LV ejection fraction (*EF*) and progressive LV dyssynchrony, indicated by a large dispersion of the SD of the LV phase angle (*LVSD*). Under chronic biventricular stimulation EF had improved <35% in three CRT responders

Discussion

This study is the first to elucidate the effects of AVD programming on ventricular resynchronisation with the use of RNV. First, we confirmed the current understanding of resynchronisation: LV dyssynchrony (SD of phase histograms) is related to the degree of contractile dysfunction (EF), while resynchronisation (characterised by a decrease in SD of LV phase histograms, Fig. 1) is related to the acute improvement in LVEF. The second finding of this study has important clinical implications: Although CRT led to an improvement in LV resynchronisation (decrease in LVSD) in all patients, this improvement was independent from the respective AVD. Thus, any AVD between 80 and 160 ms, as long as biventricular capture was preserved, led to a similar degree of improvement in mean LV resynchronisation, and this effect was also observed in patients with preserved AV conduction (Fig. 3). In fact, inter-ventricular dyssynchrony was not affected by AVD optimisation in a distinctive pattern. Therefore, the effects of AVD optimisation on LVEF, being independent of *inter*- or *intra*-ventricular resynchronisation, appear to result from individually optimised *AV* synchronisation.

This finding elucidates an important mechanism of resynchronisation: As long as biventricular capture is preserved, the intrinsic electrical activation within the His-Purkinje system has no major impact on timing of ventricular systolic contraction. The global activation imaging provided by RNV, which is averaged over a large number of cardiac cycles, is an excellent tool to evaluate any impact of AVD programming on ventricular resynchronisation.

Major effects of AVD optimisation on cardiac performance in conventional [11] and biventricular pacing [12] are known in decades. However, the effect of different AVD programming on *intra*- and *inter*-ventricular resynchronisations has not been elucidated. Our study suggests indirectly that the benefit of AVD optimisation results from improved timing of atrial systole. This hypothesis, namely the fact that AV resynchronisation plays an important role in CRT, is in line with recent studies comparing different pacing modes (i.e.

Table 2 Results of AVD optimisation on EF, inter- and intra-ventricular synchronisations

	CRT off	AVD 80	AVD 100	AVD 120	AVD 140	AVD 160	Indiv. AVD at best EF
EF (%)	26.4±6.5	28.1±7.6	27.4±7.8	28.5±8.5	28.0±7.3	28.5±7.3	30.5±7.4*
Inter-D	14.8±19.8	10.5±25.6	9±27.2	10.8±27.5	9.2±25.3	8.7±25.0	10.4±24.9
LV avr	177.8±18.7	173±20	176±20	173.3±14.6	174.8±14.6	171.5±16.3	172.5±17.9
LVSD	76.0±14.5	66.1±13	66.5±13	67.2±11.8	68.4±11.5	67.6±11.2	66.2±13.8*
RV avr	163.0±17.9	163.0±20	167±22	162.5±18.6	165.6±19.4	162.8±16.6	162.1±16.8
RV SD	57.5±16.2	53.6±18	56.8±15	55.6±14.3	56.9±15.5	60.2±14.4	55.3±15.9

Data are mean±SD.
EF ejection fraction, *Inter-D* inter-ventricular delay (difference mean phase angles RV–LV), *LV avr* average LV phase angle, *RV avr* average RV phase angle, *LVSD* SD of left ventricle phase histograms, *RVSD* SD of RV phase histograms, *CRT off* cardiac resynchronisation therapy, *AVD* atrioventricular delay
*p<0.01 vs CRT off

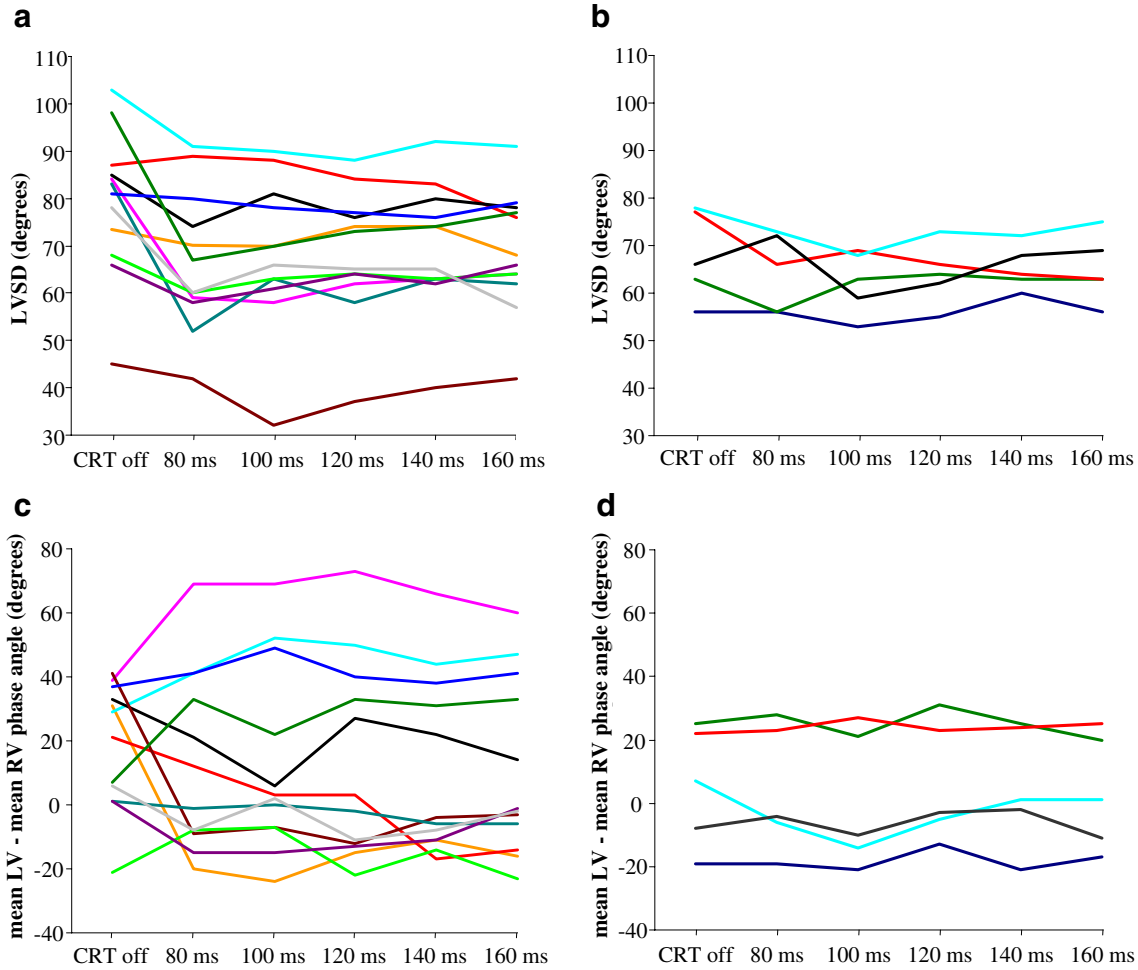

Fig. 3 Effect of different AVD on intra-ventricular resynchronisation in each patient: SD of mean phase angle in patients without (**a**) and with AVB (**b**). Effects of different AVD on inter-ventricular resynchronisation: difference of mean phase angle between right and left ventricle in patients without (**c**) and with AVB (**d**). Baseline images (CRT off) were obtained during atrial pacing with 80 ms AVD in patients without AVB and during right ventricular pacing with 180 ms AVD in patients with significant AVB (PQ intervals >250 ms or AVB third degree). *RV* right ventricular, *LV* left ventricular, *CRT* cardiac resynchronisation therapy, *SD* standard deviation

sensing only in the ventricle or sensing and pacing in all chambers) [13] and analysing PR intervals when performing inter-ventricular and AVD optimisations [14].

RNV for measurement of dyssynchrony and resynchronisation

Reproducibility of LVEF and cardiac dyssynchrony in heart failure remains challenging. Sampling a high number of cardiac beats during image acquisition in RNV equalises beat-to-beat variability and the effects of respiration. By using automatic image acquisition and analysis, the measurements are less operator dependent than with echocardiography. The quantification of inter- and intra-ventricular dyssynchrony by comparing SD of phase histograms has been successfully demonstrated and proven to be of prognostic relevance [8]. Finally, RNV integrates the entire cardiac motion, which is the ultimate goal of the latest echocardiographic techniques as well [15].

Study limitations

A major limitation of RNV is that mitral regurgitation is not taken into account and improved LVEF, therefore, does not necessarily translate into a better forward flow. This might explain some discrepancies between our findings and those from echocardiographic studies: In the present study, the magnitude of baseline LV dyssynchrony did not predict acute changes in LVEF, and the best LVEF was observed in a wide range of AVD including baseline rhythm in one patient. However, we used RNV to measure global ventricular resynchronisation reliably and reproducibly during AVD optimisation. Another limitation might be that true electrical fusion between intrinsic conduction and biventricular pacing was not studied. The absence of significant changes in CRT performance with AVD up to 160 ms, which was significantly shorter than the average baseline AV conduction, argues against a significant effect of electrical fusion. In daily clinical routine, AVDs are usually programmed below 160 ms.

Conclusion

RNV is helpful in optimising pacing parameters for CRT and provides important pathophysiologic information. Varying AVD did not have a major impact on *intra*- or *inter*-ventricular resynchronisations. Thus, the benefit of AVD-based LVEF optimisation seems to result from atrioventricular resynchronisation.

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